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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/557,537

11/21/2005

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EXAMINER

BERNHARDT, EMILY B

ART UNIT

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1624

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/557,537	Applicant(s) DAVIES ET AL.	
	Examiner EMILY BERNHARDT	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period **will** apply and **will** expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply **will**, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
 4a) Of the above claim(s) 1-3 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 4-19 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>11/21/05</u> . | 6) <input type="checkbox"/> Other: ____. |

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Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-3, drawn to compounds of formula I.

Group II, claim(s) 4-19, drawn to compounds of formula II and process of making.

Whichever Group is elected applicants are further required to elect a single species.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: They relate to compounds of considerable structural dissimilarity such that there is no special technical feature in common which can be considered the advance over the art.

During a telephone conversation with Ms. Ayler on 7/24/08 a provisional election was made with right of traverse to prosecute the invention of II, claims 4-19 and in particular the 1st species in claim 7. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-3 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

However, when a preliminary search was attempted for just the indole core with varying R5 and other variables, it would not run to completion. A sample search showed many anticipatory species when R5 was (un)substituted alkyl. Additionally, the various R choices (which include hetero rings) are variously classified such as in 544/373 when piperazine is present at R2 or 548/430 when indole is methylenedioxy-fused or 546/277.4 when R5 is pyridine, etc. Also in view of the differing issues of patentability that exist for compounds within Group II as evidenced at the very least by the art cited by applicants as well as the examiner, the restriction of Group II has been modified as set forth below.

IIA. Claims 4,5 and 8-17 when R5= choice (a)-(c);

IIB. Claims 4-6 and 8-17 when R5= choice (d);

IIC. Claims 4-19 when R5= (e); and

IID. Claims 4-6 and 8-17 when R5= choice (f).

Applicants' elected species falls within Group IIC. Applicants are advised that the claims will be examined fully with respect to the elected species and further to the extent necessary to determine patentability of the elected group.

Claims 4-5 and 8-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Scope of "substituted" appearing throughout the R variables including as an optional substituent for R5 is of unclear scope since definition in specification is open-ended. Note the wording "which includes" and "not limited to" appearing in the

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specification beginning on p.9 . A similar issue was present in Ex parte Remark 15 USPQ 2d 1498 (at p.1500) in which it was decided that claim language that relied on open-ended language was “vague and uncertain” since it was not clear what else was intended to be covered.

Claims 4-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the quinolin-2-one compounds described in Fraley (US 6,306,874) which is incorporated by reference herein, does not reasonably provide enablement for remaining compounds covered by Formula II. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. On p.12 of the specification a passing statement of utility is mentioned as “KDR kinase inhibitors” for “substituted indoles”. In the next paragraph Fraley is mentioned for teaching compounds that can be made by the instant process. An inspection of Fraley shows at best compounds of the type being claimed in claim 6, 4th species on p.27 which corresponds to instant R5 as quinolin-2-one. There is otherwise no guidance as to what type of activity remaining scope of “heterocyclyl” rings at R5 coupled with remaining “R” permutations possess. See MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art. Also note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a), August 2000 edition, which includes factors such as:

1) Breadth of the claims- the claims cover compounds easily in the billions given the huge scope of het rings permitted at R5 as well as elsewhere coupled with the

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scope of “substituted” derivatives permitted at every ring position as well as fused indole derivatives;

2) Level of unpredictability in the art- the invention is identified as pharmaceutical in nature directed to the inhibition of a biological process, namely a particular type of kinase (KDR). It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved” and physiological activity is generally considered to be unpredictable. See *In re Fisher* 166 USPQ 18. No data is reported in the specification or a clear statement that compounds made have been found active as KDR kinase inhibitors;

3) Direction or guidance- only compounds in Fraley (US’874) are shown to have kinase inhibitory activity and these represent a small portion of that claimed herein;

4) State of the prior art- The compounds are 2- heterocyclyl-substituted indolyl derivatives for which the prior art does **not** evidence the many structural permutations permitted in the instant scope are useful for one or more pharmaceutical activities;

5) Working examples- As no test data has been presented there is thus no clear evaluation of which functional groups at various positions out of the many claimed might affect potency to a large or small degree.

In view of the above considerations, this rejection is being applied.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 4-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Fraley (US'874) cited by applicants. Fraley describes at least one compound within the instant scope in all of claims 4-6. See species on line 15 in col.8 which particularly anticipates 4th species on p.27 of claim 6. There are many other compounds in Fraley that anticipate generic claims 4 and 5. See remaining species in the columns and the claims.

Claims 4,5,8 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Tollari (cited by applicants). Tollari describes the preparation of indoles instantly embraced by reductive catalysis of o-nitrostyrenes in the presence of a Pd source and ligand such as 3,4,7,8 tetramethyl phenanthroline. See in particular reaction (3) on p.207 which makes 2-(pyrid-2-yl)indole.

Claims 4,5 and 8-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Kuethe (2 references provided by the examiner). Both articles describe the preparation of a variety of 2-substituted indoles employing Pd (OAc)₂ and triphenyl phosphine. See schemes 1 and 3 in the 1st cited article and scheme 1 and Table 1 in the 2nd.

It is recognized that applicants are claiming benefit under 35 USC 119(e) which would antedate both Kuethe references. However, benefit of earlier US provisional case

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is not being granted since the claims rejected herein do not comply with 35 USC 112, par.one for the reasons given above in the 112 rejection. See MPEP 706.02, section V, part (D).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuethe references in view of Tollari and Akazome. The teachings of Kuethe as discussed in the above 102 rejection are incorporated herein. Claims 11 and 12 require use of particular ligand(s) not taught in Kuethe. Tollari and Akazome both provided by applicants teach a variety of ligands can be employed for making 2-substituted indoles. Tollari teaches the 2nd choice in claim 11 as well as use of a molar ratio well within the broad range embraced in claim 12. See Table 3 which reports a ratio of amine to Pd as 2 which inversely would be 0.5. In Akazome see various ligands taught in Table 1 which includes bipyridine with varying molar ratios taught. Thus it would have been obvious to one skilled in the art at the time the instant invention was made to modify the ligand used by Tollari with those recited in claim 11 and vary the molar ratio to those encompassed by claim 12 in view of the secondary teachings which teach successful preparation of indoles under a variety of Pd-catalyzed conditions.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Emily Bernhardt/

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